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Sjögren's Syndrome with Acute Renal Failure

We experienced a 65-year-old woman with Sjögren's syndrome who presented with acute renal failure, hypergammaglobulinemia with monoclonal gammopathy, and hypocomplementemia. She improved with steroid pulse therapy (methylprednisolone 0.5 g/day for 3 days). This patient had also sensorineural hearing loss, symmetric sensory polyneuropathy of legs, and interstitial lung disease. Ten months after recovery from acute renal failure, low-dose oral prednisolone (0.1 mg/kg/day) was withdrawn. On the third month of steroid withdrawal, acute renal failure recurred with hypergammaglobulinemia, hyperamylasemia, and autoimmune cholangitis-like biochemical derangements, which also responded to steroid pulse therapy (methylprednisolone 0.3 g/day for 3 days). When we would withdraw steroid in a patient with visceral involvement of Sjögren's syndrome, we should consider multiple clinical and laboratorial variables, including erythrocyte sedimentation rate, serum levels of IgG, total protein, C3/C4, CRP, amylase, lipase, and alkaline phosphatase. We report this case which exhibited various unusual manifestations with a review of literature.

Key Words: *Sjögren's syndrome; Kidney failure, acute; Paraproteinemias (monoclonal gammopathy); Amylases; Complement*

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INTRODUCTION

Sjögren's syndrome is a chronic inflammatory autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands, resulting in keratoconjunctivitis sicca and/or xerostomia, and B lymphocyte hyperreactivity (1-4). A small number of patients may develop serum and urine monoclonal light chains, and malignant lymphoma (1-4). Extraglandular organs, including skin, kidney, liver, lung, and nervous system may also be involved (1, 2). Approximately one-third of the patients present with renal manifestations (1, 2). Renal involvement in Sjögren's syndrome usually consists of mild and often subclinical tubular dysfunction such as defective urinary concentration ability and renal tubular acidosis, and tubulointerstitial nephritis (1, 2, 5, 6). Severe interstitial nephritis resulting in renal failure is rare (5, 6).

We experienced a case of Sjögren's syndrome presented with acute renal failure, hypergammaglobulinemia with monoclonal gammopathy, hypocomplementemia, sensorineural hearing loss, sensory polyneuropathy of legs, and interstitial lung disease. The patient improved with steroid pulse therapy. On the third month of steroid withdrawal, acute renal failure recurred with hypergammaglobulinemia, hyperamylasemia, and autoimmune cholangitis-like biochemical derangements, which responded to steroid pulse therapy. Erythrocyte sedimentation rate is the only known variable that monitors disease activity of Sjögren's syndrome. We report this case which exhibited unusual manifestations and the monitoring variables with a review of literature.

CASE REPORT

A 65-year-old woman was admitted because of generalized weakness which lasted one week. Past medical history was free of any significant diseases except a cataract operation (right eye) two years ago and tinnitus one year ago. At that time an audiogram showed sensorineural hearing loss in both ears. Two months prior to her hospitalization, routine laboratory investigations for her cataract operation (left eye) showed normal renal function and urinalysis. After operation, she complained of anorexia, nausea, vomiting, and a loss of 3 kg for two months.

On admission, she was afebrile. Blood pressure was 90/60 mmHg supine, pulse 72/min, and respiration 22/min. Abnormal clinical findings, included inspiratory crackles on one-third of the lower right lung, a dry oral

mucosa and decreased salivary flow. Direct questioning found a history of dry mouth and eyes which lasted one year, tinnitus, and paresthesia of both feet. Schirmer's test was positive.

Laboratory data showed serum creatinine 13.2 mg/dL, BUN 85.6 mg/dL, hemoglobin 12.2 g/dL, leukocyte count 10,200/mm^3 with normal differential, platelet count 408,000/mm^3, sodium 130 mEq/L, potassium 5.1 mEq/L, chloride 100 mEq/L, TCO_2 9.8 mmol/L, total proteins 7.0 g/dL, albumin 4.0 g/dL, aspartate aminotransaminase (AST) 14 IU/L, alanine aminotransaminase (ALT) 10 IU/L, alkaline phosphatase (ALP) 140 IU/L, amylase 259 IU/L (normal, 60-180), and ESR 46 mm/hr. Urinalysis revealed a specific gravity of 1.005, pH 5.0, 20-30 white cells, and 0-2 red blood cells per high-power field. The 24 hr urinary volume was 1,800 mL, protein excretion 1.3 g, glucose excretion 1.9 g, and creatinine clearance was estimated at 4.9 mL/min. Urine sodium was 30 mEq/L, potassium 14 mEq/L, chloride 20 mEq/L, osmolality 176 mosmol/kg, and fractional sodium excretion was 0.7 %. Arterial blood gas analysis showed pH 7.28, PCO_2 23.7 mmHg, PO_2 91.4 mmHg, and HCO_3 11.1 mmol/L. Chest radiograph showed bilateral interstitial pulmonary infiltrates. An echocardiogram revealed left ventricular hypertrophy with normal ejection fraction and scanty amounts of pericardial effusion. Abdominal ultrasound showed normal-sized and shaped kidneys, an increased cortical echogenicity, and no evidence of urinary tract obstruction.

Serum immunoglobulin G (IgG) was 2,111 mg/dL (normal, 650-1500), IgA 289 mg/dL (normal, 90-410), IgM 98.4 mg/dL (normal, 40-345) with monoclonal gammopathy (IgG kappa type) in serum immunoelectrophoresis. However, urine immunoelectrophoresis did not show monoclonal component. Serum C_3 and C_4 were 41.9 mg/dL (normal, 80-155) and 7.9 mg/dL (normal, 13-37), respectively. Rheumatoid factor was 22.4 U (normal, <20 U) and antinuclear antibodies (ANA) were positive with a titre of 1:80 and a speckled pattern. Anti-double-stranded DNA, anti-Sm, anti-RNP, lupus coagulant, anti-smooth muscle and anti-cardiolipin antibodies were negative. Hepatitis B and C serology, VDRL, LE cells, and cryoglobulins were negative. However, anti-SS-A and anti-SS-B antibodies were both positive. An antineutrophil cytoplasmic antibody (ANCA) test showed perinuclear staining (p-ANCA) with a titre of 1:160. Peripheral blood smear revealed normocytic normochromic anemia, reactive neutrophilia, and activated lymphocytes. Bone marrow biopsy revealed normal findings with plasma cells less than 1%. An electrophysiological study was consistent with symmetric sensory polyneuropathy.

A diagnosis of primary Sjögren's syndrome was made. On the 12th day of admission she received three boluses of i.v. methylprednisolone (0.5 g daily), followed by oral prednisolone (0.5 mg/kg per day). Eight days later she improved and serum creatinine was decreased to 3.0 mg/dL, and hemoglobin was 10.5 g/dL, total protein 5.9 g/dL, albumin 4.1 g/dL, amylase 258 IU/L, IgG 1,170 mg/dL, C_3 54.1 mg/dL, C_4 11.2 mg/dL, ESR 14 mm/hr, negative rheumatoid factor, ANA negative, and ANCA negative.

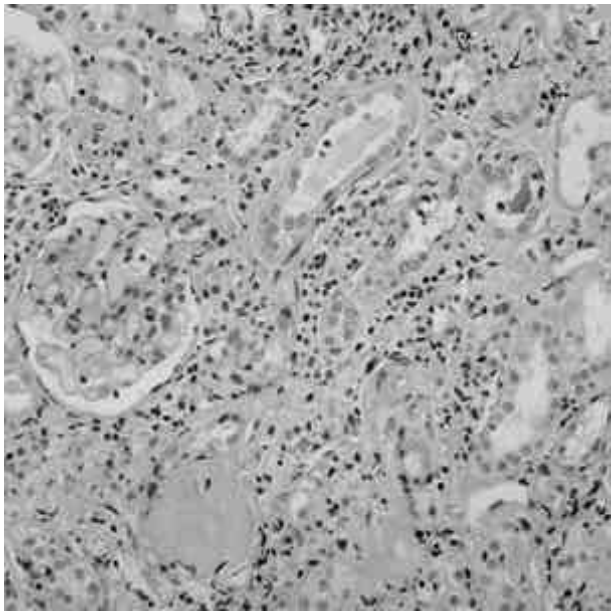

Fig. 1. Diffuse interstitial infiltration of lymphocytes and plasma cells in the cortex of the kidney (H&E, ×200).

On the 20th day of admission, renal biopsy was performed. The renal biopsy findings revealed acute interstitial nephritis, showing a diffuse infiltrate of lymphocytes and plasma cells in the cortical and medullary intersititium (Fig. 1). The infiltrate are occasionally invaded into the tubular cells. Acute tubular changes were associated; most of proximal tubules revealed loss of brush borders and were lined by flattened epithelial cells. There is focal necrosis or desquamation of tubular cells into the lumina. Mitotic figures are present in some tubules. Approximately 35% of the glomeruli (6 among 17 glomeruli) were completely sclerotic, but the remainder appeared normal in cellularity. Glomerular capillary walls and basement membranes were thin and single contoured. On immunofluorescence study, all immune reactants were negative. There were no electron dense deposits in the tubules and the glomeruli in electron microscopic study.

On the third month after steroid pulse therpy, a dose of oral prednisolone was tapered to 0.1 mg/kg per day. Laboratory data showed serum creatinine 3.1 mg/dL, BUN 35.1 mg/dL, hemoglobin 10.8 g/dL, total serum proteins 7.2 g/dL, albumin 4.8 g/dL, AST 19 IU/L, ALT

17 IU/L, ALP 105 IU/L, and ESR 10 mm/hr. Serum C_3 and C_4 levels were 61.2 mg/dL and 8.1 mg/dL, respectively. Anti-ds DNA, anti-Sm and anti-RNP were negative, but anti-SS-A and anti-SS-B antibodies were still showed positive. After ten months of steroid treatment, herpes zoster developed in the left flank and oral prednisolone was withdrawn. Laboratory data showed serum creatinine 4.8 mg/dL, BUN 49.6 mg/dL, hemoglobin 9.3 g/dL, and ESR 43 mm/hr.

On the third month after steroid withdrawal, she was readmitted to the hospital because of drowsy mental status, generalized weakness, and anorexia for 3 days. On admission, she was afebrile. Blood pressure was 100/60 mmHg supine, pulse 92/min, and respiration 22/min.

Arterial blood gas analysis showed pH 7.07, PCO_2 8.7 mmHg, PO_2 128 mmHg, and HCO_3 2.6 mmol/L. Laboratory data showed serum creatinine 12.1 mg/dL, BUN 107 mg/dL, hemoglobin 9.0 g/dL, leukocyte count 20,300/mm^3 with normal differential, platelet count 460,000/mm^3, serum amylase 684 IU/L (pancreatic isoenzyme 100%, normal, 30-60%), lipase 1,862 IU/L (normal, 0-500), total proteins 7.1 g/dL, albumin 3.5 g/dL, AST 27 IU/L, ALT 19 IU/L, ALP 432 IU/L (liver fraction, 80.6% of total), gamma-glutamyltranspeptidase (GTP) 213 IU/L, ESR 66 mm/hr, and CRP 43 mg/L. The coagulation profile was normal. Urinalysis revealed a specific gravity of 1.015, pH 5.0, 2-3 white cells, and 2-3 red blood cells per high-power field. The 24 hr urinary volume was 3100 mL, protein excretion 1.3 g, glucose excretion 10.6 g, and the creatinine clearance was estimated at 0.8 mL/min. Urine sodium was 71 mEq/L, potassium 30 mEq/L, chloride 63 mEq/L, osmolality 382 mosmol/kg, and fractional sodium excretion was 1.3%. Chest radiograph showed reticulonodular opacities in both lungs. Brain MR scan revealed only the empty sella and atrophic brain change. Abdominal ultrasound showed normal-sized and shaped kidneys with increased parenchymal echogenicity, and mild splenomegaly. Also abdominal ultrasound showed normal-sized and well-demarcated pancreas, and no evidence of cholelithiasis. An echocardiogram revealed concentric left ventricular hypertrophy with normal ejection fraction.

Serum IgG was 2,413 mg/dL, IgM 60 mg/dL with monoclonal gammopathy (IgG kappa type) in serum immunoelectrophoresis. Urine immunoelectrophoresis also showed monoclonal component (IgG kappa type). Serum C_3 and C_4 were 28.3 mg/dL and 7.6 mg/dL, respectively. ACTH was 3.6 pg/mL (normal, <37) and cortisol was 32.0 μg/dL (normal, 5-25). Rheumatoid factor was negative and antinuclear, anti-double-stranded DNA, anti-neutrophilic-cytoplasmic, anti-Sm, anti-RNP, anti-mitochondrial, anti-smooth muscle, and anti-cardiolipin antibodies were negative. Hepatitis B and C serology, HIV, VDRL, and cryoglobulins were negative. However, anti-SS-A and anti-SS-B antibodies were both positive. Lymphocyte subset assay by flow cytometry showed that total T cell was 35% of lymphocytes (normal, 60-85%) and total B cell 9% of lymphocytes (normal, 7-23%), helper cell/suppressor ratio ($CD4^+/CD8^+$) 1.0 (normal, 0.6-2.8), and natural killer cell 34% (normal, 6-29%).

Hemodialysis was instituted because of severe renal dysfunction and the occurrence of uremic symptoms (gastrointestinal and neurological). On the 3rd day of admission, she received three boluses of methylprednisolone (0.3 g daily), followed by oral prednisone (1 mg/ kg per day). One day later her mental status improved and diuresis was initiated. Serum amylase was decreased to 378 IU/L, lipase 488 IU/L, but AST was increased to 100 IU/L, ALT 55 IU/L, ALP 539 IU/L, gamma-glutamyltranspeptidase 850 IU/L, total cholesterol 128 mg/dL, and triglyceride 153 mg/dL. Eight days later serum creatinine was 2.2 mg/dL, hemoglobin 9.7 g/dL, total proteins 5.3 g/dL, albumin 3.2 g/dL, AST 235 IU/L, ALT 143 IU/L, ALP 523 IU/L, γ-GTP 796 IU/L, IgG 1,258 mg/dL, C_3 59.2 mg/dL, C_4 10.9 mg/dL, ESR 56 mm/hr, and CRP 6.7 mg/L.

On the 19th day of admission, oral mucosal biopsy showed "lymphoepithelial lesions" of the excretory duct of minor salivary gland and some lymphocytic infiltrate in the subepithelial stroma (Fig. 2). On dye injection of sialography, both parotid glands showed swelling and dilated acina, but the main ducts were not dilated. On delayed view of sialography, acini of both parotid glands

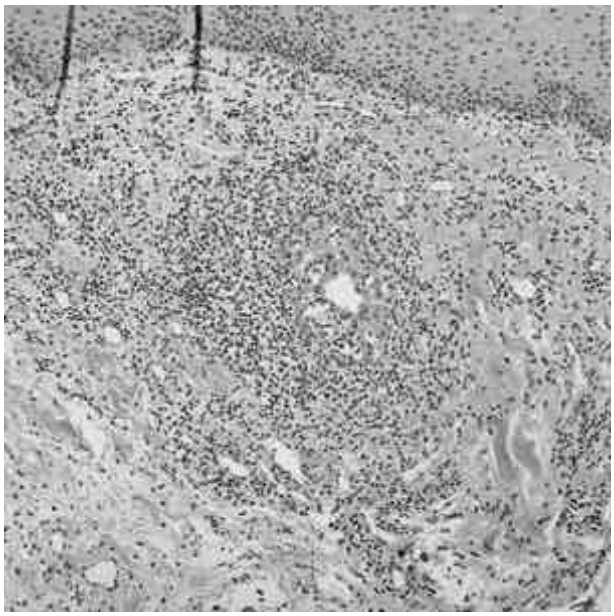

Fig. 2. Oral mucosa shows a "lymphoepithelial lesion" in the duct and surrounding dense infiltrate of lymphocytes (H&E, × 200).

and ducts were still opacified, suggesting decreased drainage capability. On the 26th day of admission, liver biopsy was performed. Liver biopsy revealed non-specific reactive hepatitis. There was mild periportal infiltration of lymphocytes and plasma cells with spotty necrosis of hepatocytes. Kupffer cell hyperplasia and an increased number of lymphocytes in the sinusoids were present. At that time, AST was 49 IU/L, ALT 62 IU/L, ALP 437 IU/L, γ-GTP 485 IU/L, total serum protein 5.67 g/L, amylase 249 IU/L, and CRP 21.2 mg/L.

On the 50th day after tapering oral prednisolone to 0.3 mg/kg per day, serum amylase and lipase reelevated. However, she was still asymptomatic, and had outpatient follow-up for 4 months without interval change.

DISCUSSION

The diagnosis of Sjögren's syndrome in this patient was made on clinical grounds such as dry eyes (positive Shirmer test) and dry mouth, and positive anti-SSA/SSB antibodies, the sialographic, and oral mucosal biopsy findings. Although hypocomplementemia is characteristic of systemic lupus erythematosus, our patient did not show other clinical or serological evidence of other associated connective tissue disease, such as systemic lupus erythematosus, rheumatoid arthritis or scleroderma. Cacoub et al. (7) presented a case of Sjögren's syndrome who had renal pseudolymphoma and hypocomplementemia. Also, p-ANCA, as in our case, have been detected in up to one-quarter of patients with Sjögren's syndrome in some series (8).

About 30% of patients wit Sjögren's syndrome have renal involvement, typically renal tubular acidosis (type I) or interstitial nephritis, associated with hypergammaglobulinemia, but the cases may be mild or poorly recognized (1, 5, 6). Clinically significant renal involvement occurs in about 10% of patients, frequently as tubulointerstitial nephropathy, and rarely as an immune complex, hypocomplementemic glomerulonephritis (2). The majority of infiltrating mononuclear cells in the kidney were CD4+ T cells (9). The mechanism of interstitial nephritis might be that T cell recognized different autoantigen-driven stimulation rather than superantigen-induced proliferation (9). Our patient presented with two episodes of acute renal failure. The cause of the first acute renal failure was confirmed as acute interstitial nephritis by renal biopsy. The cause of the second acute renal failure might be due to acute interstitial nephritis or vasculitis. Both episodes of acute renal failure responded to steroid pulse therapy. The second episode of acute renal failure occurred after two months of steroid withdrawal considering herpes zoster and her clinically stable condition. We think that withdrawing steroid in patients with Sjögren's syndrome with acute renal failure should be done carefully.

Another characteristic of our patient was hypergammaglobulinemia with monoclonal gammopathy. Sjögren's syndrome is frequently associated with both reactive and neoplastic lymphoproliferative diseases that are mostly B cell lymphoma or rarely peripheral T cell lymphoma (1, 3, 4). The primary defect in Sjögren's syndrome predisposing to lymphoma might be excessive T-helper activity with chronic B-cell stimulation and eventual escape of neoplastic B-cell clones (3). The spectrum from benign polyclonal to malignant monoclonal lymphoproliferation can occur sequentially in the same patient (4). Some clinical findings, such as a recurrent parotid swelling, splenomegaly or lymphadenopathy, and some laboratory factors such as a decrease in serum IgM level or a reduction in rheumatoid factor titer may herald the presence or development of malignant lymphoproliferation (3, 4). Because our patient had mild splenomegaly, a reduction in rheumatoid factor titer and IgM level, and monoclonal gammopathy, a follow-up was needed. Hypergammaglobulinemia of both episode in our patient decreased to normal levels after steroid pulse therapy.

Our patient showed elevated pancreatic amylase and lipase that decreased after steroid pulse therapy. On the 50th day after tapering of oral prednisolone to 0.3 mg/kg per day, amylase and lipase reelevated. However, our patient had suffered from no symptoms typical of pancreatitis or gallbladder disease. This hyperamylsemia may probably reflect a slow subclinical, inflammatory process of the exocrine pancreas (10). Recently, a serum autoantibody to a pancreatic antigen, expressed in ductal cells of exocrine gland, was identified in patients with chronic idiopathic pancreatitis and Sjögren's syndrome (11). For chronic pancreatitis associated with Sjögren's syndrome, an autoimmune mechanism may have been involved in the etiology and in which steroid therapy was effective (12). An autoimmune mechanism may have been involved in the etiology of hyperamylasemia in our patient.

Our patient also showed elevated alkaline phosphatase, elevated γ-GTP, and low serum AST. Clinical and/or biochemical evidence of liver disease is found in 5-10% of primary Sjögren's syndrome patients (1, 2). Archimandritis et al. (13) reported a case of Sjögren's syndrome with autoimmune cholangitis, who showed antimitochondrial antibody negative, antinuclear antibody (centromere pattern) positive, low to nearly normal serum IgM, low serum AST and liver histology compatible with the diagnosis of primary biliary cirrhosis. In our patient, antimitochondrial and anti-smooth muscle antibodies were negative, but transpercutaneous liver specimen revealed no specific histologic evidence. Because the early hepatic

involvement is focal, there may be a sampling error in biopsy. Another explanation for these biochemical derangements may be due to hyperamylsemia.

Our patient had sensorineural hearing loss one year before the first admission. The neurologic manifestations in Sjögren's syndrome, include central and peripheral nervous system (1, 2). Tumiati et al. (14) reported that sensorineural hearing loss is highly prevalent in Sjögren's syndrome and 64% of the patients who had sensorineural hearing loss had anti-cardiolipin antibodies. They suggested the possibility of a biological association between anti-cardiolipin antibodies and sensorineural hearing loss. However, our patient did not have anti-cardiolipin antibodies.

Our patient had the reticulonodular opacities in both lung on chest X-rays, but she was asymptomatic. Involvement of exocrine glands in the upper respiratory tract frequently leads to dryness of the nasal passage and bronchi (1, 2, 10). Pulmonary involvements include pleurisy, interstitial fibrosis, dessication of tracheobroncheal mucous membrane, and lymphoid interstitial disease (1, 2, 10).

Treatment of primary Sjögren's syndrome depends on the extent of the disease. Systemic steroids are generally reserved for life-threatening vasculitis or visceral manifestations (nervous system, lung, and kidney), hemolytic anemia, and pleuropericarditis (1, 2). Although erythrocyte sedimentation rate (ESR) was monitored to estimate disease activity in Sjögren's syndrome, the monitoring and duration of steroid treatment are still uncertain. As for the disease activity, after the second episode of acute renal failure, we monitored IgG, total protein, C3/C4, CRP, amylase, lipase, and alkaline phosphatase in addition to ESR. Among laboratory data, no single variable present which was valuable for monitoring disease activity in Sjögren's syndrome. Therefore, when withdrawing steroid in cases of the visceral involvement of Sjögren's syndrome, the multiple clinical and laboratory variables should be considered very carefully.

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